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BRAIN STIMULATION

One of the most powerful tools for the study of the interaction between brain function and behavior has been stimulation of the brain. Experimenters have applied a variety of techniques in order to induce an excitation or inhibition of the activity of the nervous system. Some of these include the introduction of chemicals and drugs into the brain. Others have employed heat and cold. However, by far, the most widely used technique has been the application of electric currents to brain tissue. The use of these various methods of brain stimulation has resulted in an impressive body of data on the structure and function of the brain and its role in the control of behavior. Using these methods, experimenters have been able to stimulate the brain in one region and record the brain's response in another region thus determining the functional connections between brain areas. Others have stimulated various brain sites and observed the overt responses of the organism under study. These responses span the range of behaviors from simple reflexes to complex patterns of responses. Still other investigators have studied the effects of stimulation of specific brain areas on ongoing behavior in order to determine whether that particular brain area is involved in the maintenance of the behavior in question. It would be an impossible task to summarize all of the various methods of stimulation which have been utilized. We will therefore, limit our discussion to the effects of electrical stimulation since this has been the method most generally employed.

The study of the effects on behavior of electrical stimulation of the brain is as old as the study of electricity itself. While observing the results of the application of electric currents to his various sense organs, Count Allesandro Volta passed the current through his own brain. He fortunately survived the experiment. Since that time,but particularly in the present century, many investigators have utilized electric currents to map pathways through the nervous system and to study the effects of stimulation of certain brain areas on behavior. Advances in electronic engineering have made available to the researcher more and more precise instrumentation and it is now possible to stimulate tiny areas deep within the brain with only minimal damage to neural tissue.

In 1870, Fritsch and Hitzig reported that an electrical stimulus applied to certain regions of the cerebral cortex could elicit movements of the face, arms, and legs of experimental animals. In 1899, Sherrington utilized electrical stimulation to demonstrate the reciprocal innervation of flexor and extensor muscles. While experiments such as these shed a good deal of light on the functioning of the reflex pathways, little was learned about voluntary behavior since exposure of such large areas of the nervous system required extensive restraint and anesthesia. The work of W. R. Hess, however, represented a major

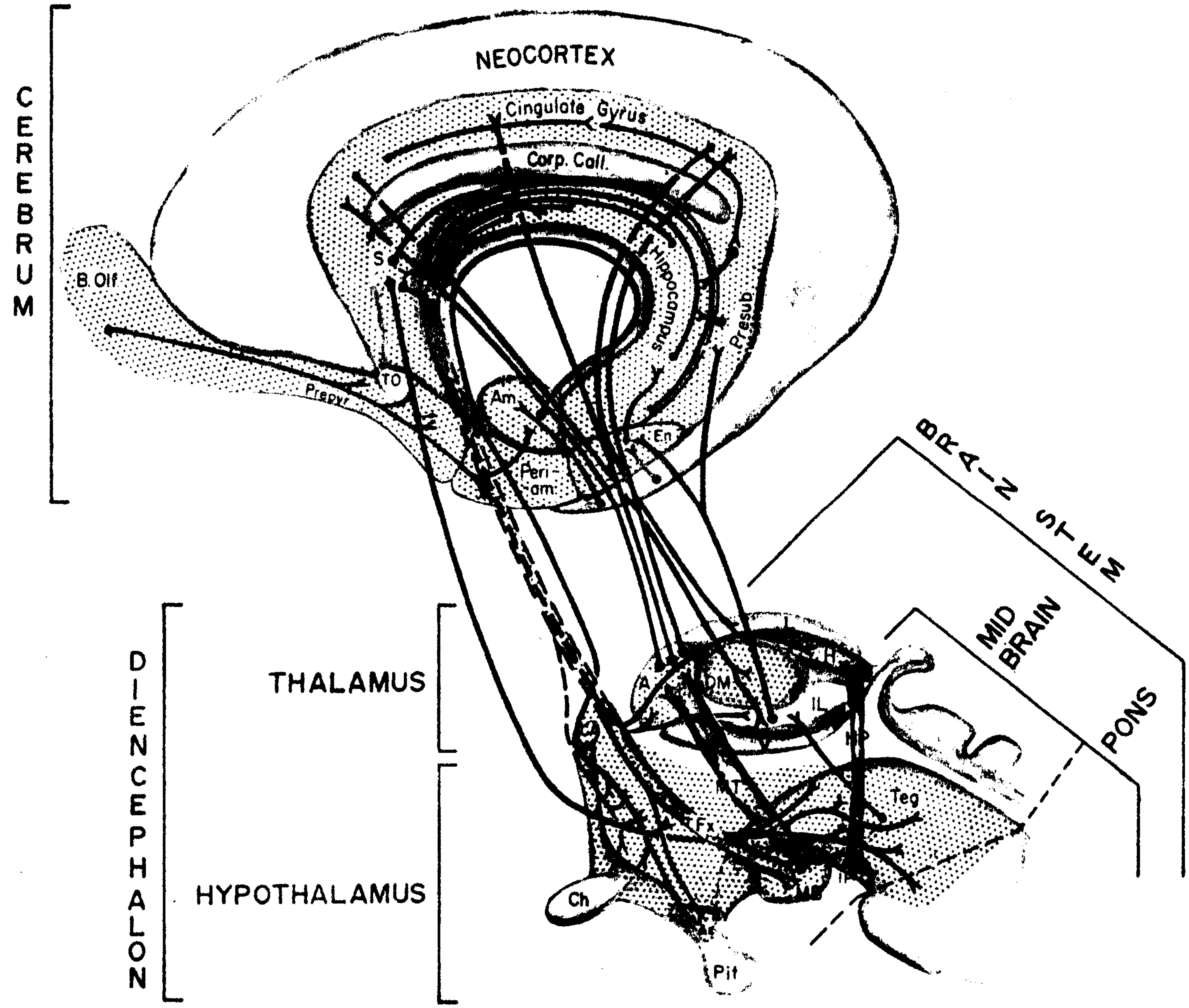
CEREBRUM
NEOCORTEX
Cingulate Gyrus
Corp. Call.
Hippocampus
Presub
S
B. Olf
TO
Prepyr
Am
En
Peri-am.
BRAIN STEM
MID BRAIN
PONS
DIENCEPHALON
THALAMUS
HYPOTHALAMUS
A
DM
H
IL
Teg
Fx
Ch
Pit

FIGURE LEGEND

Figure 1. A semidiagramatic representation of the brain. The cerebral hemisphere has been displaced from the brain stem in order to show some of the inter-connections between them. The limbic system is indicated by the stippled areas. Abbreviations: A, anterior nucleus of the thalamus; Am, amygdala; Ar, arcuate nucleus; B. Olf., Olfactory Bulb; CA, anterior commissure; Ch, optic chiasm; Corp. Call., corpus callosum; DM, dorsomedial nucleus of the thalamus; En, entorhinal area; Fx, fornix; H, habenula; HP, habenulo-interpeduncular tract; IL, intralaminar nuclei of the thalamus; IP, interpeduncular nucleus; L, lateral nucleus of the thalamus; MB, mammillary bodies (posterior hypothalamus); MT, mammillo-thalamic tract; Periam., periamygdaloid cortex; Pit., pituitary; Prepyr., prepyriform cortex; Presub., Presubiculum; S, septal region; Teg., midbrain tegmentum; TO, olfactory tubercle; V, ventral nucleus of the thalamus.

technical advance with the introduction of the first practical technique for permanent implantation of electrodes into the brain. The development of these chronic electrodes made possible the study of stimulation effects involving deep structures in awake, unrestrained, unanesthetized animals.

METHODOLOGY

Hess' electrode technique is basically the same as that used today, although many laboratories have carried out modifications to suit their own particular needs. Generally, thin, rigid, stainless steel or platinum wires, insulated except at the tip, are lowered into the brain through a small hole in the skull. The animal is deeply anesthetized. Its head is held in a metal frame called a stereotaxic instrument. This frame, a modification of a device originally conceived by Horsely and Clark (1908) not only provides firm support for the head during surgery, but also allows the experimenter to locate deep cerebral structures with a fair degree of accuracy. This is accomplished by means of a three-dimensional system of coordinates which locates any given brain structure by its position relative to some zero point. This is analogous to locating a region deep within the earth by means of its latitude, longitude, and distance from the surface. Stereotaxic atlases or brain maps of a number of common laboratory animals and man are now available. Many of these may be found in a book edited by Sheer (1961) along with illustrations of stereotaxic instruments and detailed descriptions of electrode techniques.

Due to the variability in skull dimensions from one animal to the next, the stereotaxic technique is not completely accurate, it is necessary, therefore, at the termination of the experiment to sacrifice the animal and verify the exact location of the electrode tip by microscopic examination of the brain.

Another important factor in the study of brain stimulation is the characteristics of the electrical stimulus. Generally, direct current destroys nerve tissue. Indeed, prolonged application of direct current has often been used to produce lesions for experimental or clinical reasons. However, brief pulses of direct current, alternations of positive and negative pulses, and sine waves have all been used with good results in brain stimulation studies provided that the current is not excessive.

SLEEP, WAKEFULNESS AND EMOTION

Using his technique of chronic implanted electrodes, Hess systematically explored the diencephalon of the cat (see Figure 1). He has summarized his findings in two recent works (1954a, b). In brief, Hess observed that stimulation of the massa intermedia of the thalamus resulted in a progressive decrease of activity followed by sleep. The animal could be aroused from this sleep by some external stimulus, but once the external stimulus was removed, the animal returned to sleep. Stimulation of the posterior hypothalamus, however, resulted in immediate wakefulness and a state of excitation. With stronger stimulation in this area, the cat would hiss, bare its teeth and claws, arch its back and show all the signs of rage and fear. Upon termination of the stimulation, the rage reaction ceased. Moreover, if the cat was provoked during this period of stimulation, a highly organized attack reaction would be directed towards the provocative object. Egger and Flynn (1962) have described a study, however, in which stimulation of the lateral nucleus of the amygdala suppressed the attack reaction elicited by hypothalamic stimulation.

MOTIVATION

A variety of motivational effects have been evoked by electrical stimulation of the brain, particularly in the region of the hypothalamus. Perhaps the most striking of these are the effects on food and water intake.

Food Intake

Delgado and Anand (1953) have demonstrated that cats stimulated in the lateral hypothalamic area will perform gnawing and chewing movements and will increase their food intake. It is interesting to note that the increased eating is not necessarily directed toward edible objects. Miller (1960) reports that upon presentation of stimulation to the hypothalamic feeding area, rats will gnaw on blocks of wood, sticks, etc. when food objects are not available. This behavior has been described as "stimulus-bound" eating. Miller also described a study in which rats with electrodes in the lateral hypothalamus had been trained to press a lever for food. The animals were later food-satiated and stimulated in the hypothalamus. Immediately following the onset of stimulation of the animals began to press the food lever. When the stimulation was terminated, the rats immediately stopped lever-pressing.

Suppression of food intake by stimulation has also been reported. An investigation by Wyrwicka and Dobrzecka (1960) demonstrated that stimulation of the ventromedial nucleus of the hypothalamus of hungry goats resulted in immediate cessation of eating.

Water Intake

Less work has been done in the area of central nervous system control of other motivational mechanisms by means of stimulation. Chemical stimulation of the hypothalamus has been demonstrated to effectively control water intake (Grossman, 1960). There is also evidence that electrical stimulation can influence the thirst mechanism (Anderson and McCann, 1955).

Sexual Behavior

Vaughan and Fisher (1962) have demonstrated that stimulation of the lateral anterior hypothalamus results in a marked increase in sexual capacity in male rats. McLean and Ploog (1962) have reported that stimulation of a number of forebrain and diencephalic areas in monkeys results in erection of the penis and ejaculation.

LEARNING

The application of the techniques of intracranial stimulation to the study of the neuropsychology of learning has been a fruitful one. The typical approach has been to compare the performance of experimental organisms with and without stimulation of some neural areas, on a learning task. This method has advantages over the traditional lesion technique which requires elaborate control groups to assess the possible extraneous effects of surgical shock, blood loss, intracranial pressure, etc. In a stimulation study, each animal frequently serves as its own control, since the effects of stimulation are almost always reversible. However, certain learning tasks may necessitate the use of a control group with non-stimulated electrodes. Experiments employing electrical stimulation of the brain to study learning are numberous. A few examples of recent investigations may serve to illustrate some of the major trends in current research.

Delayed Alternation and Visual Discrimination

Rosvold and Delgado (1956) trained monkeys to perform a delayed alternation task in which the animals were required to seek a peanut reward under the right food cup on one trial, under the left food cup on the next trial, under the right on the next, etc. A five-second delay was interposed between trials. Failure to alternate responses on successive trials was regarded as an error. The monkeys were also trained to perform a simple visual discrimination. Following stabilization of performance on these tasks, the monkeys were implanted with multiple-lead electrodes. Upon recovery from surgery, the animals were again tested on the delayed alternation and visual discrimination problems. During a part of the testing session, electrical stimulation was delivered through one of the electrode leads. The experimenters found that performance declined markedly on the delayed alternation test when the lead stimulated was in the caudate nucleus. However, the same stimulation failed to interfere with the visual discrimination task. A later study by Buchwald, et.al. (1961) revealed that stimulation of the caudate nucleus does interfere with acquisition of a visual discrimination task, but does not alter performance once the task has already been learned.

Operant Conditioning

In another type of experiment, Knott, et.al., (1960) trained cats to press a lever for meat reward in a modified Skinner box. Electrodes were implanted in a number of deep cerebral structures. Continuous low intensity stimulation was delivered during the lever-pressing task. The experimenters report that stimulation of the hippocampus, caudate nucleus and thalamus failed to alter the lever-pressing rate. Stimulation in the septal area, however, resulted in a cessation of responding during stimulation. The animals returned to the lever following termination of the stimulation, but only after a prolonged delay. Hypothalamic stimulation generally had the same effect as septal stimulation, except that the post-stimulation delays were shorter. The authors concluded that these data support the notion that certain neural pathways, critical to the mechanisms of learning and retention,become "occluded" by the stimulation. The data, however, could also be interpreted in terms of interfering emotional responses evoked by stimulation of the hypothalamus and septal area.

Classical Conditioning

A third type of investigation utilizes the classical Pavlovian conditioning paradigm with the exception that both the conditioned stimulus (CS) and unconditioned stimulus (US) are presented to the subject by means of implanted electrodes. Doty and Giurgia (1961) implanted electrodes in the motor area of the cerebral cortex of dogs, cats and monkeys. Stimulation of these electrodes served as the US. The unconditioned response was the particular limb movement which resulted from the stimulation of a direct motor pathway. Stimulation in some other cortical area served as the CS. Six to ten pairings of the CS and the US were made daily. The experimenters were able to demonstrate clear-cut evidence of conditioned reflexes with cortical stimulation as the Us.

Aside from their implications for learning theory, the experiments of Doty and Giurgia are important because they suggest the possibility of studying the electrophysiology of the conditioning mechanisms in a simple form with known and well defined inputs.

SPEECH AND MEMORY

A series of remarkable experiments have been carried out by Penfield and his associates. These investigations have involved the electrical stimulation of the cerebral cortex of awake humans. The studies were carried out during the course of neurosurgical procedures for the treatment of epilepsy. During the operation, the comfort of the patient was maintained at all times by the careful administration of local anesthesia. In addition to yielding highly detailed maps of sensory and motor regions of the human cerebral cortex, this research has also indicated the location of areas which are involved in the mechanisms of speech and memory. Penfield has described regions on the temporal lobe in which electrical stimulation will result in the recall of vivid memories of sights and sounds. The patients report that they feel as if they were reliving those events. Moreover, a specific memory can be repeated by interrupting the stimulation and then quickly reapplying it. Penfield suggests that memory is organized on the temporal lobe in somewhat the manner in which electrical impulses representing visual and auditory patterns are stored on magnetic tape. Thus, whenever a particular region of the brain is made to yield up its stored memories, the memories are recalled with the same vividness and clarity as when they were originally stored. He further suggests the existence of mechanisms in the brain which inhibit the retrieval of those stored memories and that the electrical stimulation somehow bypasses or otherwise nullifies the influence of these inhibitory mechanisms.

Penfield and his co-worker have also mapped areas of the cortex which upon stimulation result in vocalization, interference with speech and complete arrest of speech, hisitation and distortion of speech and repetition of vocal sounds. In addition, stimulation of certain areas results in an inability to name specific objects while the remainder of the speech mechanism seems to be unimpaired. These areas are mainly included in the parieto-temporal-occioital cortex, although the effects have also been obtained from several other well defined cortical regions.

SELF-STIMULATION

In an attempt to study the effects of subcortical stimulation on learning in rats, Olds and Milner (1954) placed a rat with a forebrain electrode in an open field maze. They observed that if the rat received stimulation in a particular place in the maze, it would spend more and more time in that place. The stimulation seemed to have a rewarding effect on the rat's behavior. Next, they placed the rat in a T-maze. The animal learned to go to that arm of the maze in which it was rewarded with brain stimulation. Microscopic examination of the rat's brain revealed that the electrode tip was in the vicinity of the anterior commissure. Subsequent rats were trained to deliver the stimulation to themselves by pressing a lever in a Skinner box. These animals would deliver several hundred stimulations per hour to themselves. The stimulation served as the sole reward for pressing the lever. Food and water were never present in the box.

Since the original report by Olds and Milner, many of the variables affecting the self-stimulation phenomenon have been explored. Some of the principal variables have been the animal species, the location of the electrodes in the brain, the intensity, frequency and duration of stimulation, the motivational and emotional state of the organism, and the schedule of reward. In addition, the effects of drugs on self-stimulation have also been studied.

Species

Self-stimulation of the brain has been clearly demonstrated in the following species: rat, dog, cat, pigeon, monkey, dolphin, guinea pig, goldfish and man. At this point, experimenters would be more interested in learning of a species in which the phenomenon could not be demonstrated than further additions to the list of positive instances.

The demonstration of self-stimulation in man is of particular interest since this is the only species which can give us verbal reports about the subjective experience of brain stimulation. Sem-Jacobsen and Torkildsen (1960) have reported cases in which electrodes were implanted in the brains of human patients for several months in the course of treatment for Parkinson's disease. During exploratory stimulation, the experimenters encountered several regions of the forebrain in which the patients seemed to enjoy the stimulation. They would smile or grin and express a desire for repeated stimulation. If given an opportunity to press a button to deliver the stimulation to themselves, the patients would press the button often. Their verbal reports ranged from descriptions of "tickling" sensations to expressions of satisfaction and euphoria.

Anatomical Variables

In general, self-stimulation has been demonstrated in those structures of the brain which form part of the limbic system (see Figure 1) or have strong anatomical, connections with it (Olds,1956). The effect of stimulation in purely sensory or motor areas does not appear to have any rewarding effect. Moreover, there are areas in which the effect of the stimulation appears to be punishing, and animals will learn to escape and avoid stimulation in these areas (Brown and Cohen, 1959). Many of these negative regions correspond to those areas which, upon stimulation produce rage and attack reactions.

Within the positive reward system, rates of self-stimulation vary widely from area to area and from species to species. Thus, a rat may self-stimulate 800 to 1,000 times per hour in the septal area, 2,000 per hour in the hypothalamus, and 4,000 per hour in the tegmentum. Furthemore, the reported rates of responding may vary considerably between laboratories due to differences in apparatus. For example, higher response rates are possible with a telegraph key lever than with a microswitch lever.

If an animal presses a lever 1,000 times per hour for septal stimulation and 2,000 per hour for hypothalamic stimulation, it is safe to conclude that the hypothalamic stimulation is more rewarding to the animal? An experiment by Hodos and Valenstein (1962) suggest that this may not necessarily be. Rats were given a choice, in a two-lever box, between septal stimulation and hypothalamic stimulation. These were presented at various intensities. When presented with high intensity septal stimulation on one lever and low intensity hypothalamic stimulation on the other lever, the animals showed a clear preference for the lever producing septal stimulation even though their response rates were much higher on the lever producing hypothalamic stimulation. Considering these findings, it would seem hazardous to draw general conclusions about the relative reward values of stimulation in different neural areas based solely upon rate of responding. Direct preference tests at several intensities of stimulation provide data which are less subject to interpretive ambiguities resulting from the interfering influence of motor side-effects produced by the stimulation.

Stimulation Variables

Reynolds (1958) demonstrated that as the intensity of stimulation increased, rate of responding increased, passed through a maximum, and then declined. Keesey (1962) confirmed this finding and, in addition, reported similar effects with variation in stimulation frequency and duration.

This decline in self-stimulation rate with high intensities of stimulation should not necessarily be interpreted as a decline in the rewarding properties of the stimulation. Hodos and Valenstein (1962) reported that when given the choice between two intensities of stimulation in the same area, rats consistently chose the higher of the two intensities, even though they self-stimulated at a lower rate for the higher intensity.

Motivational Factors

Brady, et.al. (1957) observed that animals would self-stimulate faster when deprived of food or water than they would when they were satiated. This was later confirmed by Olds (1958) who further reported that injections of male sex hormone in castrated male rats also increased the rate of electrical self-stimulation. However, Hodos and Valenstein (1960) failed to find any effects on septal self-stimulation rate of injection of female sex hormones in spayed female rats. Recently Hoebel and Teitelbaum (1962) have demonstrated an interesting correlation between the hypothalamic areas controlling feeding behavior and those yielding self-stimulation. They suggest that the feeding system may control self-stimulation in a manner similar to its control of food intake.

Pharmacological Effects

Olds, et.al. (1956) as well as other workers have demonstrated that some drugs can affect self-stimulation performance. Chlorpromazine and Reserpine, both tranquilizing drugs, each depressed the self-stimulation rate in some areas, but not in others. However, phenobarbital was not observed to produce any specific effect on performance.

Emotion

Brady and Conrad (1960) demonstrated an interesting effect of self-stimulation on emotional behavior. Rats were trained to press a lever for either intracranial stimulation or water reward. Periodically, an auditory stimulus was presented for a period of five minutes. At the termination of this stimulus, a painful electric foot-shock was administered to the animals. When the animals were pressing the lever for water, presentation of the auditory stimulus produced a clear suppression in the rate of responding described as conditioned "fear" or "anxiety" in previous studies. No conditioned "fear" response to presentation of the auditory stimulus could be elicited, however, when the animals were lever pressing for brain stimulation in the medial forebrain area. Moreover, the possibility that the animals were unable to hear the auditory signal during the brain stimulation has been eliminated by Beer and Valenstein (1960) who showed that rats could with little difficulty, make auditory discriminations when the auditory signals were present stimultaneously with brain stimulation.

Reward Schedules

Sidman, et. al. (1955) have presented data illustrating the point that behavior rewarded by brain stimulation on fixed ratio schedule or variable interval schedule generally has the same characteristics as food-rewarded behavior on the same schedules. However, Brodie, et.al. (1960) have reported that fixed ratios of higher than 20 responses for each stimulation are difficult to maintain in monkeys unless very slow and gradual training is permitted. Fixed ratios of several hundred responses for each reward are not at all uncommon when animals are rewarded with food. Moreover, these workers report far less resistance to extinction of the brain stimulation-rewarded performance than has often been observed on equivalent food-rewarded schedules.

In a study of timing behavior, Brady and Conrad (1960) required monkeys to space their responses at least twenty seconds apart in order to receive a reward. In the case of food reward or anterior thalamic stimulation reward, the animals had no difficulty in delaying their responses for the required period of time and thereby received a large proportion of the possible rewards. The most frequent inter-response time was twenty seconds. However, in the case of stimulation of the globus pallidus, the animals were unable to delay their response sufficiently and thereby received few rewards. The most frequent inter-response time was ten seconds. There is some suggestion that the stimulation may have interfered with the mechanism of time perception in these animals.

SOME GENERAL PROBLEMS

When an experimenter produces a change in behavior by stimulation of a brain area, there is a great temptation to speculate on the possible role of that area in the mechanisms underlying the behavior. However, such speculation should be made cautiously for the electrical stimulus may not have the same effect on all neural areas. For example, we have seen that stimulation of the caudate nucleus results in a deficit in delayed alternation performance and that stimulation of the amygdala suppresses rage reactions. These behavioral deficits are the same as the effects of lesions in those neural areas. Therefore, it seems likely that the electrical stimulation had a suppressing effect upon normal function. On the other hand, we have seen that electrical stimulation of the lateral hypothalamus yields eating responses while ventromedial hypothalamic stimulation results in suppression of eating. These effects are the opposite of those observed when lesions are made. Presumably, in this case, the stimulation was augmenting the activity of the feeding areas. Thus, the effects of stimulation studies alone are not sufficient for determining the role which a cerebral structure may play in behavior.

A second and related problem is that of attempting to generalize from the highly unphysiological type of stimulation which experimenters introduce into the brain to the normal types of physiological events present in the nervous system. The former may not necessarily have the same effect on neural tissue and cautious interpretation of data is required. Perhaps more electroencephalographic studies during brain stimulation will shed some light on the utility of this generalization.

A third problem is that of the possible interaction between brain stimulation and other environmental variables which may be affecting the behavior under study. We have seen that caudate nucleus stimulation will markedly interfere with visual discrimination performance if the animal is still in the process of acquiring the discrimination. However, the effects will be scarcely detectible once the animal has mastered the problem. Similar difficulties may arise in the study of emotional behavior, memory and perception. Therefore, a thorough knowledge of the environmental variables which influence behavior is essential before attempting to study the effects of stimulation on behavior.

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